Title: *BRCA1*- and *BRCA2*-Associated Hereditary Breast and Ovarian Cancer *GeneReview* – Probability Models for *BRCA1*/*BRCA2* Pathogenic Variants

Authors: Petrucelli N, Daly MB, Pal T

Updated: December 2016

Note: The following information is provided by the authors and has not been reviewed by *GeneReviews* staff.

Probability Models for BRCA1/2 Pathogenic Variants

Each has its unique attributes determined by the methods, sample size, and population used to create it. These models include those using logistic regression, genetic risk models using Bayesian analysis (BRCAPRO and Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm [BOADICEA]), as well as empiric data such as the Myriad prevalence tables.

The validity of several of the models has been compared in different studies, and the data show that these models perform reasonably well in typical breast-ovarian cancer families seen in cancer genetics clinics [Antoniou et al 2008]. Most models do not include other *BRCA*-related cancers (e.g., pancreatic cancer, prostate cancer). Interventions that decrease the likelihood that an individual will develop cancer (such as oophorectomy and mastectomy) may influence the ability to estimate the probability of a *BRCA1/2* pathogenic variant [Katki 2007]. Furthermore, one study has shown that the models are sensitive to the amount of family history information available and do not perform as well with a limited family structure, defined as having fewer than two first- or second-degree female relatives surviving beyond the age of 45 years in either lineage [Weitzel et al 2007].

The performance of the models can vary in specific ethnic groups as well [Oros et al 2006, Vogel et al 2007, Kurian et al 2008, Kurian et al 2009] suggesting that further information is needed to determine which model performs best in each ethnic group. More recently, the addition of breast tumor markers including estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2/neu) has been shown to improve the performance of BRCAPRO and BOADICEA [Tai et al 2008, Mavaddat et al 2010, Biswas et al 2012].

As more individuals have undergone molecular genetic testing of *BRCA1* and *BRCA2*, risk assessment models have improved. Nevertheless, there is an art to risk assessment and thus, probability models cannot replace clinical judgment. Also, it is important to note that there are factors that could limit the ability to provide an accurate risk assessment (i.e., small family size, few female relatives, and/or risk reducing surgeries).

Table. Characteristics of Common Models for Estimating the Likelihood of a *BRCA1/BRCA2* Pathogenic Variant

	Myriad Prevalence Tables [1]	BRCAPRO [2]	BOADICEA [3]	Tyrer-Cuzick [4]
Method	Empiric data from Myriad Genetics based on personal and family history reported on requisition forms	Statistical model, assumes autosomal dominant inheritance	Statistical model, assumes polygenic risk	Statistical model, assumes autosomal dominant inheritance
Features of the Model	Proband may or may not have breast or ovarian cancer	Proband may or may not have breast or ovarian cancer	Proband may or may not have breast or ovarian cancer	Proband must be unaffected
	Considers age of breast cancer diagnosis as <50 y or >50 y	Considers exact age at breast and ovarian cancer diagnosis	Considers exact age at breast and ovarian cancer diagnosis	Also includes reproductive factors and body mass index to estimate breast cancer risk
	Considers breast cancer in ≥1 affected relatives only if diagnosed <50 y	Considers prior genetic testing in family (e.g., *BRCA1/2* - negative testing)	Includes all FDR and SDR with and without cancer	
	Considers ovarian cancer in ≥1 relative at any age	Considers oophorectomy status	Includes AJ ancestry	
	Includes AJ ancestry	Includes all FDR and SDR with and without cancer		
	Very easy to use	Includes AJ ancestry		
Limitations	Simplified/limited consideration of family structure	Requires computer software and time-consuming data entry	Requires computer software and time-consuming data entry	Designed for individuals unaffected with breast cancer
	Early age of breast cancer onset	Incorporates only FDR and SDR; may need to change proband to best capture risk and to account for disease in the paternal lineage	Incorporates only FDR and SDR; may need to change proband to best capture risk	
		May overestimate risk in bilateral breast cancer [5]		
		May perform better in whites than minority populations [6]		
		May underestimate risk		

		of *BRCA2* pathogenic variant in high-grade serous ovarian cancers but overestimate the risk for other histologies (REFERENCE)		

From National Cancer Institute Genetics of Breast and Ovarian Cancer (PDQ®)
BOADICEA = breast and ovarian analysis of disease incidence and carrier estimation algorithm
FDR = first-degree relatives
SDR = second-degree relatives
AJ = Ashkenazi Jewish
Y = years
1. Frank et al [1998]
2. Parmigiani et al [1998], Katki [2007]
3. Parmigiani et al [1998], Antoniou et al [2004]
4. Tyrer et al [2004]
5. Ready et al [2009]
6. Huo et al [2009], Kurian et al [2009]

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